AKKAMAHADEVI WOMEN'S UNIVERSITY

VIJAYAPUR-586108

RESEARCH PROPOSAL

On

"STUDIES ON SYNTHESIS AND BIOLOGICAL EVALUATION OF HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN "

Research proposal submitted to the Department of Pharmaceutical chemistry for registration of Degree of

Doctor of Philosophy

In

Pharmaceutical Chemistry

Submitted by

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INTRODUCTION

Heterocyclic compounds constitute one of the most important classes of organic compounds. Many heterocyclic compounds occur naturally and their functions are often of fundamental importance to living systems. Heterocyclic compounds are having a cyclic structure with at least two different kinds of atoms in the ring, generally one is carbon and the most common heteroatoms present are nitrogen, oxygen and sulfur. Heterocyclic compounds with rings containing other heteroatoms are also known. The heterocyclic ring may contain one or more than one heteroatom which may be alike or unlike. Heterocyclic compounds may be composed of more than one ring of which at least one must be a heterocyclic ring. Many of such heterocycles contain oxygen, nitrogen and sulfur as hetero atoms in their structural frame.

Heterocyclic compounds are of great synthetic interest because of their wide distribution in nature and useful biological activities'. Heterocycles such as furan, pyrrole and thiophene are versatile pharmacophore possessing a variety of biological and pharmacological activites[2,3].

Oxygen heterocycles, five membered heterocyclic system, i.e., furan has been investigated to large extent. Furan ring when fused with carboxylic systems such as benzene and naphthalene gives condensed heterocycles, benzofuran and naphthofuran.

Thiophene heterocycle, a five membered heterocyclic system contains sulfur as a heteroatom. Thiophene ring when fused with carboxylic systems such as benzene and naphthalene gives condensed heterocycles, benzothiophene and naphthothiophene.

Pyrrole ring when fused with carboxylic systems such as benzene gives condensed heterocycles, indole. Pyridene ring when fused with carboxylic systems such as benzene gives condensed heterocycles, quinoline.
The following are main heterocyclic compounds

1.Benzofuran
2.Naphthofuran
3.Benzothiophene
4.Naphthothiophene
5.Indole
6.Quinoline

1.BENZOFURAN

Benzofuran is a unique scaffold that is associated with several biological activities. The numerous synthetic benzofuran derivatives have been synthesized and found to possess wide range of biological activities, such as antiviral[4], antimicrobiar[5,6], anti-inflammatory[7], antianalgesic[8] and antidiabetic[9].

2.NAPHTHOFURAN

Naphthofurans possess a broad range of biological activities[10,11] that are constituents of important natural products. Many of the derivatives of naphthofuran have been extracted from various plants.

The first synthesis of naphthofuran was reported by Stoermer[12]. The regioisomeric naphthofurans are present in many biologically important natural products, mainly belonging to the class of sesquiterpenes[13].

Many compounds involving a naphthofuran ring have attracted much attention, in view of their diverse pharmacological properties. Several synthetic compounds bearing this ring skeleton are associated with diverse biological activities such as antimicrobial[14] anthelmintic[15] anti-inflammatory[16,17], diuretic[18], analgesic[19], antineoplastic[20] , anti-convulsant[21] , anti-viral[22] , genotoxic[23,24] and anticancer[25].

3.BENZOTHIOPHENE

Thiophene belongs to a class of heterocyclic compounds containing a five membered ring made up of one sulphur as heteroatom. Thiophene and its derivatives exist in petroleum or coal. Thiophene structure can be found in certain natural products and is also incorporated in several pharmacologically active compounds.

Thiophene was discovered as a contaminant in benzene[26]. The simple thiophenes resemble corresponding compounds of benzene in boiling points and in odour.Thiophene and its derivatives are important heterocyclic compounds that are widely used as building blocks in many agrochemicals and pharmaceuticals[27]. The benzene ring of a biologically active compounds may often replaced by a thiophene without loss of activity[28]. This is observed in

examples such as NSAID's lornoxicam, the thiophene analog of piroxicam. Lornoxiacam (chlortenoxicam) is a NSAIDs (non steroidal anti-inflammatory drugs) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties.

4.NAPHTHOTHIOPHENE

As already mentioned thiophene and its derivatives exist in petroleum or coal. This petroleum extract contains various organosulfur compounds such as thiols, sulfides, and thiophenes. Naphthothiophene are also minor components of fossil fuels. Naphthothiophenes consist of a mixture of isomers, namely, naphtho[2,l-b]thiophene , naphtho[2,3-b]thiophene , and naphtho[l,2-b]thiophene and all of them were detected in fossil fuels such as shale oils [29].

Naphtho[b]thiophene derivatives show some interesting biological activities such as antifungal[30] anti-plasmodial[31], anti-trypansoma[32] and antimalarial activities[33]. However, there are fewer approaches for the synthesis of naphtho[b]thiophenes in the Litrature[34] .

Three naphtho[b]thiophenes (asymmetric dibenzothiophene isomers) are minor components relative to the prevailing dibenzothiophene constituents of aromatic fractions of diagenetically oxidised marine sedimentary rocks. Interestingly, the rocks containing naphtho[b]thiophenes often also contain their arylated derivatives, phenylnaphtho[b]thiophenes, as major components relative to phenyl dibenzothiophenes. Both these series are accompanied by other structural isomers, i.e., naphthylbenzo[b]thiophenes[35].

5.INDOLE

Nitrogen-containing heterocycles have been used as medicinal compounds for centuries, and form the basis for many common drugs such as Resorpine, Captopril (treatment of hypertension) and Vincristine (cancer chemotherapy). The chemical structure of the flinderoles is based on the nitrogen-containing indole ring system; however, these compounds have a novel structure not reported in the literature, due to the attachment of the two indole rings. The flinderoles are related to the borreverine compounds, such as isoborreverine , but as a consequence of their more 'open' structure, the development of a new synthetic methodology for their preparation is required. Thus one of the aims of this research work is to develop novel synthetic methodology for this ring-system, to synthesise the flinderoles for further testing, and, if successful, to apply this methodology to the synthesis of other related heterocycles which may show similar or improved bioactivity.

Substituted heterocyclic compounds offer high degree of structural diversity and have been proven to be broadly useful as therapeutic agents. Thus, there is great deal of interest in the

development of strategies for generating heterocyclic libraries on solid supports. Indole derivatives have been a topic of substantial research interest and continue to be one of the most active areas of heterocyclic chemistry, particularly due to their natural occurrence and pharmacological activities. The name indole arise from the merge of the words indigo and oleum, meaning that it was isolated by treatment of natural dye indigo with sulfuric acid or sulfuric anhydride mixture.

Indoles are among the most important of all biologically active organic compounds. Replacement of indole ring by other heterocycles is often accompanied by loss of biological acivity. Indoles have been synthesized to prevent and/or treat inflammatory and autoimmune diseases including rheumatoid arthritis, diabetes mellitus, multiple sclerosis, autoimmune nephritis, and allergic inflammation[36,37] Indoles have also been studied to treat drug resistant tumors as antitumor agents on their own or for use in cotherapy to enhance the action of known antitumor drugs[38] .

Objectives of the study

The following are the main objectives of of present study

- To carry out extensive review of literature review to understand methods for synthesis of heterocycles containing nitrogen.
- Design the synthesis of some compounds fused to heterocyclic ring system.
- To characterize the synthesized compounds employing different spectral tools.
- To evaluate the synthesized compounds for their antifungal, antioxidant activity.

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